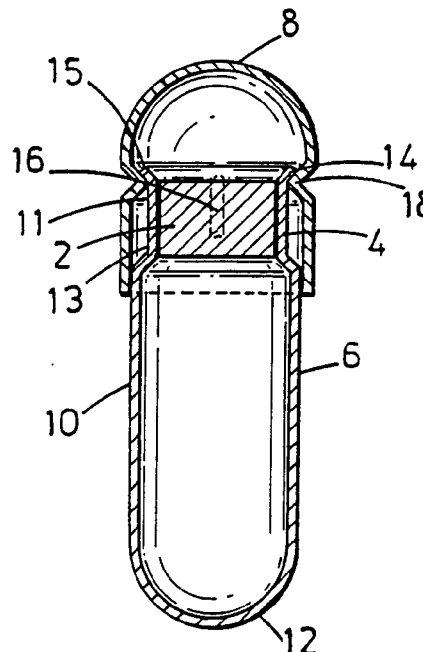




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB93/02268 <b>(22) International Filing Date:</b> 4 November 1993 (04.11.93)  <b>(30) Priority data:</b> 9223146.3 5 November 1992 (05.11.92) GB  <b>(71) Applicant (for all designated States except US):</b> R.P. SCHERER CORPORATION [US/US]; 2075 West Big Beaver Road, Troy, MI 48084 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only) :</b> RASHID, Abdul [GB/GB]; 25 Camphill Avenue, Glasgow G41 3AU (GB). STEVENS, Howard, Norman, Ernest [GB/GB]; Ballyconachy, Balmaha Road, Drymen, Stirlingshire G63 0BX (GB). BAKHSHAEI, Massoud [IR/GB]; 8 Park Avenue, Glasgow G64 2SN (GB). KELSO, James, Robertson, Miller [GB/GB]; 24 Courthill Street, Dalry, Ayrshire KA24 5AN (GB). HEGARTY, Mark [GB/GB]; 34 Alwyn Drive, Stewartfield, East Kilbride G74 4RL (GB). MACKIE, James, Leonard [CA/CA]; 3350 Dolphin Court, Windsor, Ontario N8R 2G7 (CA).		<b>(74) Agents:</b> HORNER, Martin, Grenville et al.; Cruikshank & Fairweather, 19 Royal Exchange Square, Glasgow G1 3AE (GB).  <b>(81) Designated States:</b> AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.          Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> VENTED CAPSULE  <b>(57) Abstract</b>  A controlled release capsule comprises a male plug (2) formed of a water-swellaable hydrogel which is engaged within a neck portion (4) of a female body (6). The capsule is intended to deliver a pharmaceutically active material. In contact with an aqueous medium, such as in the gastro-intestinal tract, the hydrogel plug swells and becomes disengaged from the body, thereby releasing the active material. In order to facilitate insertion of the hydrogel plug, the neck portion of the body is provided with one or more vent channels (16), which extend part-way along or the entire way along the length of the neck portion. The vent channels relieve pneumatic pressure as the plug is inserted.		



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VENTED CAPSULETECHNICAL FIELD

The present invention relates to a controlled release vented capsule construction, which comprises a male member engaged within a neck portion of a female body; the capsule including a water swellable material which swells so as to disengage the female body upon exposure of the capsule to an aqueous medium. The capsule is intended to contain a pharmaceutically active material.

BACKGROUND

International patent specification W090/09168 discloses a device of this type which comprises a water swellable male plug engaged within a female body. A pharmaceutically active material is contained within the device. When the capsule is exposed to water, the male hydrogel plug swells and eventually disengages itself from the female body, thereby allowing the pharmaceutically active material contained within the device to be released. It has been found that the time taken to release the pharmaceutical material is predictable and reproducible, so that the device may be used to release pharmaceutically active materials within the body of a patient after a predetermined time interval (e.g. 0.5 to 12 hours). This may, for example, be useful in the treatment of medical conditions where it is desirable to administer a

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pharmaceutically active material to the patient sometime through the night while the patient is asleep, so as to provide a desired level of the drug in the patient in accordance with his needs, for example during the night or when he awakes. It may also be useful to allow dosing of materials at a predetermined point as the capsule passes through the gastro-intestinal tract, for example in the colon.

Patent specification W092/13521 (Alza Corporation) describes fluid-imbibing dispensing devices for delayed delivery of an active agent, which include an expansion means which absorbs fluid from a surrounding environment. The dispensing device comprises a housing having first and second wall sections telescopically engaged with each other, particularly a capsule having a hollow cap and a hollow body; either the cap or the body is in the form of a male section fitted inside the open end of the other female section. The expansion means is contained within the device and expands as it absorbs fluid, forcing apart the two sections of the device. The expansion means may be a swellable polymer or an osmotic formulation which swells as it absorbs fluid. In order to allow fluid to come into contact with the expansion means contained within the device, one of the wall sections adjacent to the expansion means is fluid-permeable. After the sections are disengaged, fluid enters the device and comes into contact with the active agent contained within the

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device, thereby dispensing the active agent into the fluid.

Conventional hard gelatin capsules are produced and filled in large numbers using high speed automatic machinery. Such capsules comprise a body and a cap. Normally, the cap is pre-fitted to the capsule body during manufacture of the capsule. During filling, the filling machine removes the cap, fills the capsule with pharmaceutical material, and then replaces the cap in a manner such that the cap is locked onto the capsule body. Patent specification US 3,399,803 discloses a self-locking medicament capsule wherein the body has a groove near its open end and the cap at the corresponding ridge which snaps into the groove so as to lock the cap and body together. US 4,442,941 discloses a bayonet-type arrangement whereby a raised portion on the cap is engaged into a groove on the body.

European patent specification 246804 also discloses a capsule body having a groove near its mouth for the purposes of preventing the capsule distorting from its cylindrical form, which may cause difficulty in fitting the cap onto the capsule body.

A preferred embodiment of the controlled release capsule with which the present invention is concerned (and as disclosed in W090/09168) requires that a male member (such as a hydrogel plug) be a close fit within the neck of the female capsule body so that the male member is firmly retained and does not detach prematurely. The

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hydrogel plug prior to hydration is a fairly rigid material. For these reasons, it may be difficult to insert the tightly fitting hydrogel plug into the mouth of a conventional cylindrical capsule body using high speed machinery. In view of the tight-fitting nature of the plug, there may be a build up of pneumatic pressure within the female body as the plug is inserted, which may tend to impede insertion.

It is an object of the present invention to mitigate this problem.

#### SUMMARY OF THE INVENTION

The present invention provides a controlled release capsule which comprises a male member engaged within a neck portion of a female body; the capsule including a water swellable material which swells so as to disengage the female body upon exposure of the capsule to an aqueous medium; the female body having an entrance, and the neck portion having a first end nearer said entrance and a second end farther from said entrance; and a vent channel extending from said first end of the neck portion at least partially along the neck portion so as to allow venting from the capsule body during insertion of the male member into the neck portion.

Generally, the female body and the neck portion thereof are of substantially cylindrical configuration according to conventional practice.

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The vent channel may extend the whole way down the neck portion. In this case, the channel remains open after insertion of the plug, and this construction is largely limited to filling of the capsule with solid materials, such as granules or tablets. Where the capsule is to contain a liquid or a flowable material such as a powder, it is preferred that the vent channel should only extend part way down the neck so that when the plug is inserted fully, it seals with an area of the neck into which the vent channel does not extend.

Usually, at least two vent channels are provided.

The vent channel may be of any suitable cross sectional configuration, such as semi-circular, triangular, square, etc. The channel may extend parallel to the longitudinal axis of the capsule or at an angle thereto; or even in a helical arrangement. The shape and configuration of the vent channel may also be chosen to provide a degree of resilience within the cylindrical neck region which assists insertion and retention of the plug. In some cases, insertion of the plug may cause distortion or even substantial elimination of the vent channel.

The neck may be narrower or wider than the remainder of the body, or of the same width. When the neck portion has the same width as the remainder of the body, the vent channel extends outwardly from the line of the capsule body by, for example, 5 to 10% of the body width. When the neck portion is narrower than the remainder of the

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body, the vent channel may be 5 to 10% of the width of the neck portion.

The walls of the female body may be formed from a wide variety of materials. They may be of homogenous constructions or they may be laminated. Examples of materials suitable for use in the construction of the body include polyethylene, polypropylene, poly(methylmethacrylate), polyvinyl chloride, polystyrene, polyurethanes, polytetrafluoroethylene, nylons, polyformaldehydes, polyesters, cellulose acetate and nitro cellulose.

However, a preferred construction uses an impermeable coating to cover the exterior of a body which has been formed from a water soluble material. The coating may conveniently be formed by dipping the body in a solution of a material which forms a layer which is impermeable to water. Alternatively, the body might be spray-coated. A preferred class of capsule bodies are conventional hard gelatin or starch capsule bodies coated with a solution of polyvinyl chloride or a polyvinyl acetate copolymer or an ethyl cellulose solution.

In a preferred embodiment, the male member is a plug formed of said water swellable material, such that as the plug swells it disengages from the female body. The plug is preferably formed of a water-swellable hydrogel, such as described in W090/09168.

In another embodiment, the male member is a hollow



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member closed at one end, whose opposite open end engages within the neck of the female body. A water swellable material is provided within the capsule which serves to disengage the female body after a predetermined time, by forcing the male member and the female body apart as the material swells in the presence of water. The swellable material inside the capsule may be an osmagent or an osmopolymer. Such an arrangement is disclosed in WO92/13521. In order to allow water to enter the capsule and to contact the water-swellable material a portion of the wall of the capsule adjacent thereto is preferably semipermeable; that is to say it is permeable to the passage of water into the capsule but impermeable to release of other substances from within the capsule.

#### DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Embodiments of the present invention will now be described by way of example only in conjunction with the drawings wherein;

Figure 1 is a cross-sectional elevation of a first embodiment;

Figure 2 is a view from above with the cap removed; and

Figure 3 is a partial elevational cross-section of a second embodiment.

The capsule shown in Figures 1 and 2 comprises a male member in the form of a plug 2 formed of a hydrogel

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material, inserted in neck 4 of female body 6. The capsule is closed with a cap 8.

The body 6 comprises a cylindrical main portion 10 and closed end 12. The main body narrows to the neck portion 4 which is substantially cylindrical so as to receive the male plug 2 with a close tolerance. The neck portion then flares out to a flared mouth portion 14 which has an entrance 15 of a diameter substantially the same as the diameter of the main body portion 10. The neck portion has a first upper end 11 adjacent the flared mouth portion and the entrance, and a second lower end 13.

The cylindrical neck portion is provided with a vent channel 16 shown in dotted lines which extends from the flared mouth portion part way down the neck portion and allows the release of pneumatic pressure from within the capsule body during insertion of the plug. However, the vent channel extends only part way down the neck portion, so that when the plug is fully inserted into the neck, it seals with the lower region of the neck where the vent channel is absent. Thus, venting will only occur until the lower end of the plug passes the lower end of the vent.

As shown in Figure 2, a vent channel 16 may be provided on both sides of the neck as required.

The male plug 2 is formed of a hydrogel material (such as disclosed in WO 90/09168) and is usually inserted so that the upper end of the plug is level with or below the upper end of the capsule body. Whether the plug is

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inserted proud of the neck portion, flush with the upper end of the neck portion, or is recessed below the upper end of the neck portion can affect the time taken to expell the plug. This time will be chosen according to the desired release time of the capsule contents.

The capsule is then sealed with the cap 8 which is provided with detentes 18 which clip under the rim of the flared mouth portion thereby locking the cap in place.

The cap is formed of a water soluble material, such as gelatin. The capsule body is formed of a water insoluble material, which may be a water insoluble plastics material or may be gelatin coated with a water-impermeable coating.

The capsule body is formed in conventional manner by dipping a mould pin into a gelatin solution and allowing to dry. The gelatin is coated with a water-impermeable coating (e.g. by dip-coating), after the capsule body has been stripped from the mould pin and trimmed to size. Alternatively, the water-impermeable coating may be applied by spray coating or vapour deposition. The cap 8 is then temporarily fitted over the capsule body such that the detentes 18 do not lock over the rim of the flared mouth portion. The pre-assembled empty capsule is then stored for later filling. During filling, the cap is removed from the capsule body, and a pharmaceutically active material is filled into the capsule body. The hydrogel plug is then fitted into the neck of the body.

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Finally, the cap is replaced over the end of the capsule body and pushed down so that the detentes 18 clip over the rim of the flared mouth portion, thereby locking the cap in place.

However, the preassembly step is not essential. The caps and bodies may be stored separately and fed separately to the filling machine, particularly if precautions are taken to prevent the caps nesting together and the bodies nesting together during storage and feeding in the filling machine.

When the capsule is administered to a patient, the aqueous environment in the gastro-intestinal tract quickly dissolves the water soluble cap. Water is then absorbed into the hydrogel plug 2, which swells and is expelled from the body after a predetermined time interval (for example 2 to 10 hours). This allows the contents of the capsule to be released into the patient's system gastro-intestinal tract.

Figure 3 shows a second embodiment which is similar to the first embodiment, except as regards the shape of the flared mouth portion and the extent of the vent channel.

Thus, the vent channel 17 extends through the full length of the cylindrical neck portion, so that even when the plug is fully inserted, a total seal is not achieved. Such a construction may be easier to demould than the shorter channel shown in the previous embodiment.

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The flared mouth portion 14 is belled outwardly, such that the region of the entrance region 15A to the body portion is substantially cylindrical and of a diameter substantially the same as that of the main portion 10. The facilitates location of the plug in the mouth of the body prior to being fully inserted.

Variations may be made. Thus, the narrow neck region 4 can be replaced by a neck region which is wider than the main body portion 10; or by a neck region of substantially the same width as the main body portion 10.

CLAIMS

1. A controlled release capsule which comprises a male member (2) engaged within a neck portion (4) of a female body (6); the capsule including a water swellable material which swells so as to disengage the female body upon exposure of the capsule to an aqueous medium; the female body having an entrance (15), and the neck portion having a first end (11) nearer said entrance and a second end (13) farther from said entrance; and a vent channel (16) extending from said first end of the neck portion at least partially along the neck portion so as to allow venting from the capsule body during insertion of the male member into the neck portion.
2. A capsule according to claim 1 wherein the vent channel (16) extends part-way along the neck portion such that when the male member is engaged within the neck portion the male member seals with a portion of the neck adjacent said second end into which the vent does not extend.
3. A capsule according to claim 1 wherein the vent channel (17) extends along the full length of the neck portion.

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4. A capsule according to any preceding claim wherein the vent channel extends substantially parallel to a longitudinal axis of the neck portion.
5. A capsule according to any preceding claim wherein the vent channel is substantially semi-circular in cross-section.
6. A capsule according to any preceding claim wherein the vent channel extends outwardly from the neck portion by 5 to 10% of the width of the neck portion.
7. A capsule according to any preceding claim wherein there are at least two vent channels.
8. A capsule according to any preceding claim wherein the neck portion of the female body is substantially cylindrical and is narrower than the remainder of the body.
9. A capsule according to any preceding claim wherein the male member is a plug and the plug is formed of said water-swellaable material.

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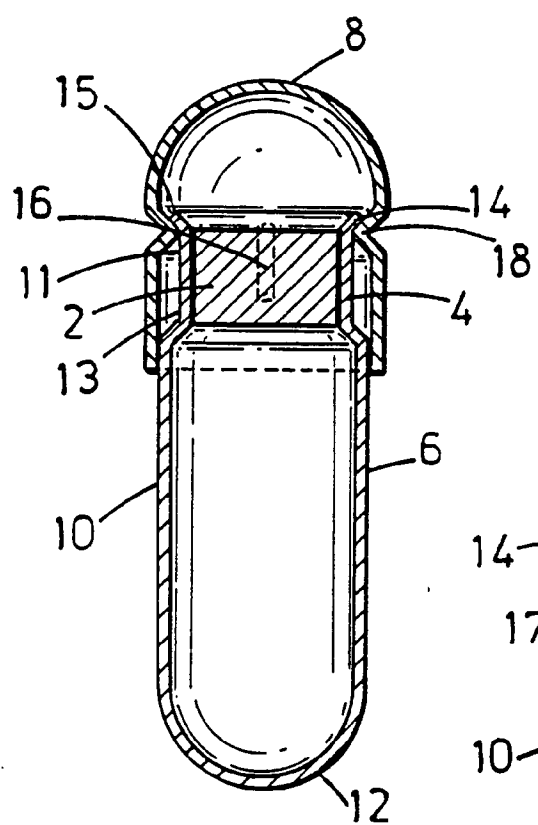


FIG. 1

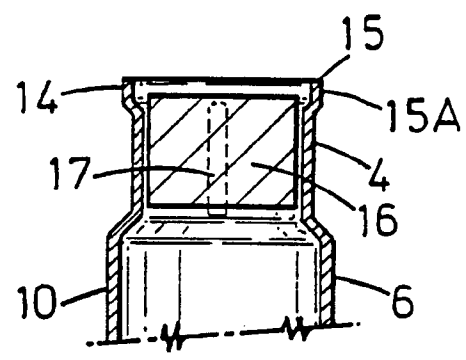


FIG. 3

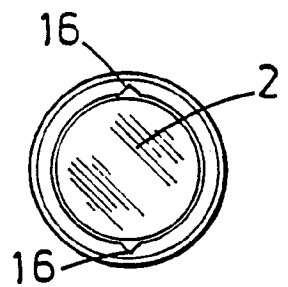


FIG. 2



## INTERNATIONAL SEARCH REPORT

Inter national Application No

PCT/GB 93/02268

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 A61J3/07

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61J A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,90 09168 (NATIONAL RESEARCH DEVELOPMENT CORP.) 23 August 1990 cited in the application see abstract ---	1
A	DE,A,22 32 236 (PARKE) 31 January 1974 see page 4, paragraph 3 - page 5, paragraph 2; figures 6,7 ---	1,2,4
A	US,A,4 793 493 (MAKIEJ) 27 December 1988 ---	
A	GB,A,2 148 235 (WARNER-LAMBERT) 30 May 1985 -----	

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 93/02268

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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DE-A-2232236	17-01-74	NONE	
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